

New Technologies for Liver Disease

NOTE: The Solicitations and topics listed on this site are copies from the various SBIR agency solicitations and are not necessarily the latest and most up-to-date. For this reason, you should use the agency link listed below which will take you directly to the appropriate agency server where you can read the official version of this solicitation and download the appropriate forms and rules.

The official link for this solicitation is: <http://grants.nih.gov/grants/guide/pa-files/PA-09-094.html>

Agency:

Department of Health and Human Services

Release Date:

February 11, 2009

Branch:

n/a

Open Date:

February 11, 2009

Program / Phase / Year:

STTR / Phase I / 2009

Application Due Date:

January 08, 2012

Solicitation:

[PA-09-094](#)

Close Date:

January 08, 2012

Topic Number:

1

Description:

Liver and biliary diseases affect Americans of all ages and all walks of life. Collectively liver and biliary diseases rank in the top 10 causes of mortality in the United States. Chronic liver diseases affect between 5 and 10 percent of Americans and account for 1 to 2 percent of deaths in the United States. Gallbladder disease affects an estimated 20 million Americans and causes considerable morbidity and occasional mortality. Liver cancer currently ranks 8th as a cause of cancer deaths and has been increasing markedly as a cause of cancer in the United States over the last decade. Yearly economic costs for chronic liver disease and cirrhosis are estimated to be \$1.6 billion, for liver cancer \$1.3 billion and for gallbladder disease \$6 billion.

Liver and biliary diseases can be caused by infectious agents, inherited defects, metabolic disturbances, alcohol, toxins and environmental toxicants. The most common causes of liver diseases are chronic hepatitis C, alcohol liver disease, nonalcoholic fatty liver disease, chronic hepatitis B, autoimmune liver diseases and drug-induced liver diseases. Many of these conditions can be prevented or treated, but if not, they can lead to progressive liver injury, liver fibrosis and ultimately cirrhosis, portal hypertension, end-stage liver disease and, in some instances, liver cancer. Currently, the only therapy for end-stage liver disease is liver transplantation. More than 5000 liver transplants are done in the United States each year (including more than 500 in children). At least 17,000 persons are on a waiting list for liver transplantation and as many as 1500 die yearly while waiting. The needs and challenges in liver disease research are many.

In February 2005, the Digestive Diseases Interagency Coordinating Committee of the National Institutes of Health (NIH) released a trans-NIH Action Plan for Liver Disease Research. The text of this Action Plan is available on the NIH website at: <http://liverplan.niddk.nih.gov>.

The major purpose for development of the Action Plan was to identify areas of greatest scientific opportunity to serve as a stimulus to progress and help direct NIH research resources toward practical but important goals in the prevention and control of liver and biliary diseases. The Action Plan outlined a total of 214 research goals categorized into 16 areas of liver disease research. Many of these research goals are appropriate for Small Business Innovative Research Grants and represent excellent opportunities for translational research that could be conducted by a small business with expertise and interest in biomedical research. This announcement summarizes these opportunities and defines the interest of the sponsoring Institutes and Centers in funding such research.

Summary of Priority Areas

The objective of this FOA is to encourage and enable scientists at small businesses to develop and evaluate new technologies, drugs, devices, and approaches to diagnosis, management, and prevention of liver disease. Development of new technologies as well as application of existing technologies may be proposed. Studies may include use of animal models or human participants or both. If appropriate, plans for manufacturing and clinical evaluation of developed technologies, drugs, devices and innovative approaches should be included in the application. However, clinical trials beyond Phase I studies will not be considered appropriate to this announcement.

Appropriate topics for development and validation under this FOA include, but are not limited to, the following which are categorized into four major areas and which incorporate research goals from the Action Plan for Liver Disease Research:

Diagnostic Assays. A specific diagnosis can be made in most liver diseases but may require specialized testing or an invasive procedure. In some instances, diagnostic assays are not generally available and may lead to delay or mistakes in diagnosis. More accurate, commercially available tests are needed for several liver diseases and conditions.

- Simple screening assay for Wilson disease that might be applied to newborns and/or adolescents and adults with this disease.
- Non-invasive means of assessing copper or iron content of the liver.
- Commercially appropriate molecular tests for diagnosis of the forms of progressive familial intrahepatic cholestasis (caused by mutations in FIC1, BSEP or MDR3).
- Accurate and reproducible diagnostic test for acetaminophen toxicity and alcoholic liver disease.

Biomarkers and Imaging Techniques. Biomarkers and more sensitive imaging techniques may allow for non-invasive means of assessing the liver and obviate the need for liver biopsy in diagnosis, staging and grading of liver diseases.

- Non-invasive biomarkers and imaging methods for liver **fibrosis** that accurately reflect the stage of liver disease and can detect mild to moderate degrees of fibrosis before the onset of cirrhosis. Biomarkers could be individual tests on serum or urine or a combination of tests that might be applied in an algorithm to assess degree of fibrosis.
- Molecular signatures of major forms of **hepatotoxicity** for diagnostic use during genomic, proteomic and/or metabolomic technologies.
- Non-invasive imaging techniques for visualization of the **biliary tree** for architecture, motility, inflammation and cancer.
- Non-invasive biomarkers or imaging techniques for **inflammation and injury** in the liver that accurately reflect the activity of liver disease and thus might be used to assess the need for therapy or the adequacy of ongoing therapy.
- Non-invasive biomarkers or imaging methods for the degree of **fat** in the liver that provide a reliable quantification of steatosis. Biomarkers that can reliably separate simple fat

- (steatosis) from fat accompanied by liver injury (steatohepatitis) as well as distinguish fat accumulation due to alcoholic and nonalcoholic causes are particularly needed.
- Non-invasive biomarkers and imaging methods for assessment of **liver regeneration** that can be applied to living donor liver transplantation to both donor and recipients or to patients with severe acute liver injury such as to provide a reliable assessment of the likelihood of recovery and help in the decision to attempt liver transplantation.
 - Non-invasive biomarkers for assessment of **immune tolerance** or adequacy of immune suppression that could be applied to patients after liver transplantation to guide the dose of immunosuppressive therapies and whether therapy can be safely withdrawn. Biomarkers for adequacy of immune suppression and tolerance are also needed in management of autoimmune liver disease to guide dose of prednisone or other immune suppressive agents and the possibility of drug withdrawal.
 - Non-invasive biomarkers and imaging techniques for early and reliable detection of **hepatocellular carcinoma** and **cholangiocarcinoma**. Patients with cirrhosis or advanced chronic liver disease are at high risk for hepatocellular carcinoma and simple, but reliable, serum or urine screening tests are needed to identify liver cancer at an early stage while better imaging techniques are needed to reliably separate benign, regenerating nodules from cancer. Similarly, in patients with chronic biliary disease such as sclerosing cholangitis or intrahepatic gallstones are at high risk for development of cholangiocarcinoma, and serum or urine assays for early detection and imaging tests for reliable identification of this tumor are greatly needed.
 - Non-invasive biomarkers for **hepatotoxicity** due to medications, herbals, environmental chemicals or nutritional supplements. Currently, serum aminotransferase levels are used to monitor or assess liver toxicity from medications, but some elevations in these liver-associated serum enzymes occur commonly but are self-limited and do not signal significant liver injury. More reliable markers for significant liver injury that might be combined with serum aminotransferase levels are needed.
 - Non-invasive biomarkers of exposure to specific environmental chemicals that cause liver toxicity that could be used to predict future onset of **hepatotoxicity** and to be able to distinguish hepatotoxicity from transient adaptive enzyme elevations.
 - Determination of individual liver metabolizing enzyme SNP profiles in animals and humans that could be used to assess sensitivity to specific drugs and environmental exposures.

Pharmacotherapy. Safer and more effective disease-specific as well as non-specific therapies for liver disease are needed. Understanding of pathways of liver cell injury, repair, and regeneration are likely to lead to new and innovative approaches to treat liver diseases.

- Drugs, biologics, complementary and alternative modalities or molecular therapies that inhibit liver cell injury nonspecifically through inhibition of necrosis or **apoptosis**.
- Drugs, biologics, complementary and alternative modalities or molecular therapies that safely promote **regeneration**, particularly in the situation of living donor liver transplantation
- Drugs, biologics, complementary and alternative modalities or molecular therapies that inhibit **fibrosis** or promote **fibrolysis** in chronic liver diseases.
- Drugs, biologics, complementary and alternative modalities or molecular therapies that provide liver cell **cytoprotection** and might be appropriate for therapy of hepatotoxicity or chronic hepatitis.
- Drugs, biologics, complementary and alternative modalities or molecular therapies that ameliorate **itching** in chronic liver disease through interruption of the pathways that lead to pruritus.
- Drugs, biologics, complementary and alternative modalities or molecular therapies that **reduce portal pressure** in different stages of the development of cirrhosis and portal hypertension.
- Drugs, biologics, complementary and alternative modalities or molecular therapies for the effective noncytotoxic therapy for **hepatocellular carcinoma**.
- Drugs, biologics, complementary and alternative modalities or molecular therapies that **inhibit fat accumulation** in the liver.
- Drugs, biologics, complementary and alternative modalities or molecular therapies that

- **inhibit recruitment of inflammatory cells** in the liver.
- Improvement in current therapy for acute crisis of the hepatic **porphyrias**.
- Development of small molecule therapeutics for **viral hepatitis B, C, and D** that are also effective in the post liver transplant period.
- Dietary supplements for the therapy of alcohol related liver diseases through the NIAAA such as **silymarin, s-adenosylmethionine, betaine, folate, and zinc**.

Gene Therapy. Gene therapy holds enormous promise for therapy and potential cure of many inherited as well as acquired liver diseases. Advances in gene therapy could well replace liver transplantation for several liver diseases.

- Better and safer vectors for gene therapy of liver **diseases**.
- Means of improving homing of vectors to the liver.
- Improved techniques of gene delivery and cell transplantation.

Liver Assist Devices. Currently there are no means of providing support to liver function in the face of liver failure or after major hepatectomy. Liver assist devices could be life-saving as a bridge to liver transplantation (while awaiting an appropriate donor liver) in a patient with primary graft non-function or acute liver failure or while awaiting the normal processes of regeneration to occur in acute liver failure or delayed regeneration after partial hepatectomy.

- Develop techniques for culture of primary hepatocytes in large volumes with sustained functions.
- Develop artificial hepatic assist device using either primary human hepatocytes, primary mammalian hepatocytes, transformed human hepatocytes or continuous liver cell lines.